UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,259	01/26/2004	Xiao-Chun (Chris) Le	033110-004	6473

21839 7590 09/17/2008

BUCHANAN, INGERSOLL & ROONEY PC
POST OFFICE BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
09/17/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/763,259	LE, XIAO-CHUN (CHRIS)	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,11,12,16 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4, 11-12, 16 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 2-4, 11-12, 16 and 24 are pending and under examination.

Withdrawn Rejections

In view of the amendments to the claims and applicant's declaration, the 35 USC 102 rejection over Wan has been withdrawn.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claim 24 as amended, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record as reiterated below.

Non-sequitur in claim 24 of "**the** laser-induced fluorescence polarization".

Response to Arguments

Applicant argues that with the amendment to claim 24, this rejection has been obviated.

In reply, claim 24 has not been amended to obviate the above rejection. For example, claim 24 step (c)(i) recites: "determining ***the*** laser-induced fluorescence polarization of the separated binding complex; (ii) comparing the laser-induced fluorescence polarization of the binding complex with the laser-induced fluorescence polarization of the unbound probe; and (iii) comparing the result obtained in step (i) with the result obtained in step (ii), wherein the binding complex exhibits increased polarization compared to unbound probe and allows detection of the binding complex. The preceding recitation in the claim does not refer to any laser-induced fluorescent polarization. Furthermore, the claim is unclear as to step (iii) and seems repetitive.

Claim Rejections - 35 USC § 103

Claims 2-4, 11-12, 16 and 24, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Laing (6,331,392) in view of Le et al (6,132,968) for reasons of record and repeated below.

Laing discloses (throughout the Patent disclosure) at e.g., the abstract, a method for screening for bioactive compounds in particular those that bind to RNA sequences by assessing the stability and/or the conformation of an RNA target in the

presence and absence of test ligands (complex formation, as claimed), and identifying as a ligand any test ligand that causes a measurable change in target RNA stability and/or conformation. The effect of a ligand on target RNA stability and/or conformation is assessed by measuring the fluorescence polarization of a fluorescently labeled probe. Probes include molecules, which comprise fluorescent moieties whose measurable fluorescence properties, particularly polarization are sensitive to the stability and/or conformation of the target RNA as reflected in the binding state of the probe. Probe is any molecule to which a fluorescent moiety is attached, in which one or more fluorescence properties are sensitive to the stability and/or conformation of the target RNA and/or to the binding state of the probe. Suitable probe compounds include without limitation nucleic acids, particularly oligonucleotides; small RNA-binding molecules exemplified by 2-deoxystreptamine antibiotics, which bind the Rev-responsive element in HIV RNA, or other compounds that specifically recognize the major or minor groove of RNA; and proteins, and peptides derived therefrom, that recognize particular RNA sequences or conformations. See also Fig. 1. Test ligands may be derived from large libraries of synthetic or natural compounds. For example,

synthetic compound libraries are commercially available. See the specifics of the method in Example 1.

Laing further discloses at e.g., col.3, lines 15-21:

> Probes useful in practicing the invention include molecules which comprise fluorescent moieties whose measurable fluoresence properties, particularly polarization or anisotropy, are sensitive to the stability and/or conformation of the target RNA as reflected in the binding state of the probe.

Laing further discloses the stoichiometry i.e., ratios at e.g., col.8, line 1 up to col. 9, line 20:

> …determination of the absolute amounts or ratios of stabilized and non-stabilized or folded and unfolded target RNA may be carried out using probes which comprise one or more fluorescent moieties. Any stability-sensitive and/or conformation-sensitive probe to which an appropriate fluorescence moiety can be attached may be used in practicing the invention. For example, an oligonucleotide can be designed so that it will hybridize to a particular RNA target only when the RNA is in an unfolded conformation or to single-stranded regions in an otherwise folded conformation.

Laing does not disclose the use of capillary electrophoresis as recited in claim 2. However, Le discloses, throughout the Patent disclosure, electrokinetic chromatography by incorporating the teachings of Hjerten at e.g., col. 18, lines 45-57:

> The specificity of the methods provided herein is further enhanced by the use of capillary electrophoresis to separate fluorescent and non-fluorescent molecular entities. Capillary electrophoresis is described by Hjerten et al., U.S. Pat. No. 5,114,551, the entire contents of which are hereby incorporated by reference. Capillary electrophoresis includes the use of capillaries which are filled either with a gel (e.g., polyacrylamide) or with buffer. The use of capillary electrophoresis in the methods

> of the invention provides rapid sample analysis and permits the use of small sample volumes, making it particularly useful for analyzing samples of biological interest [See, e.g., Xian et al. (1996) Proc. Natl. Acad. Sci. USA 93:86-90].

Le further discloses at e.g., col.8, lines 30-50:

> Importantly, the methods of the invention are more accurate than prior art methods since they avoid potential artifacts which are caused by chemical or enzymatic nucleic digestion. Instead, the methods of the invention limit sample manipulation to extraction of nucleic acid sequences, incubation of the extracted nucleic acid sequences with proteins which are specific for the nucleic acid modification of interest and with nucleic acid sequence modification-specific molecules, and capillary electrophoresis.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use electrokinetic chromatography(EC) as capillary electrophoresis (CE) separation in the method of Laing as taught by Le above. Le teaches that said EC, particularly, CE is an accurate method that avoids potential artifacts caused by chemical or enzymatic nucleic digestion. One having ordinary skill in the art would have been motivated to use a capillary electrophoresis in the method of Laing for the advantages derived in said use as taught by Le above. One would reasonably expect that the use of said chromatography in the method of Laing would result in the separation of the bound from unbound complex since the technique of

chromatography has been known and employed in the art for such separation. Furthermore, it would have been obvious to determine the result effective variables such as the stoichemistry of a complex(compound) and /or binding affinity and correlate the results of one technique to the other. Such correlation would expectedly provide accurate quantitative or qualitative measurement of the complex being determined.

Response to Arguments

Applicant recognizes that the method of the Le '968 patent is directed to detecting and/or quantitating at least one modification to a nucleic acid sequence of interest. Le cites the use of fluorescently labeled polypeptides as one exemplary method of identifying a modification to a nucleic acid sequence. Neither the Laing '392 patent, nor the Le '968 patent, suggest the method of the present application which provides a method for determining the binding affinity and/or stoichiometry between a binding factor and a probe by combining information obtained from electrokinetic chromatography and laser-induced fluorescence polarization. The outstanding office action asserts that it would be within the ordinary skill in the art to correlate the results between two techniques of analysis for accurate determination or

analysis of the complex to be studied, citing disclosures from Laing patent at col. 8, which states that "determination of the absolute amounts or ratios of stabilized and non-stabilized or folded and unfolded target RNA may be carried out using probes which comprise one or more fluorescent moieties." Determination of absolute amounts or ratios of stabilized and non-stabilized target RNAs differs significantly from the method of determining binding affinity and/or stoichiometry of a binding complex between a binding factor and a probe which can be achieved with the method of the present application. For example, one can determine the stoichiometry or binding ratio between a binding factor, such as a protein, and a probe. That is, one can determine whether one, two, or more copies of a particular binding factor interact with a particular probe by combining the results of the electrokinetic separation with the determination of the binding complex by laser-induced fluorescence polarization. This new, unrecognized result of combining the electrokinetic separation and the detection of the separated binding complexes by laser-induced fluorescence polarization does add new methods of obtaining information about binding complexes that was not provided by the nature and quality of the cited prior art.

In reply, attention is directed to the cited section of Laing's disclosure at e.g., col. 8, which as applicant stated taught the stoichiometry measurement (i.e., ratios) and the binding determination **at e.g., col. 3**. Thus, it would be within the ordinary skill in the art to correlate the results between two techniques of analysis for accurate determination or analysis of the complex being determined. As applicant recognized above, each of these techniques are well-known in the art. It would be within the ordinary skill in the art to use this technique separately or in combination with a reasonable expectation that the combination would successfully better identify the compound/complex under study.

> Where the combination of old elements performed a useful function, but it added nothing to the nature and quality of the subject matter already patented, the patent failed under §103. KSR v. Teleflex, 17 S. Ct. 1727, 82 USPQ 2d 1385 (2007).

Double Patenting

Claims 2, 11, 16 and 24, as amended, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 9 of U.S. Patent No. 6,132,968('968 Patent) in view of 6,331,392 ('392 Patent) for reasons reiterated below.

The claims and specification of the '968 Patent claims/discloses a method for quantitating at least one

modification of interest in a nucleic acid sequence contained in a sample, comprising: a) providing: i) a sample suspected of containing a nucleic acid sequence comprising the at least one modification of interest; ii) a first polypeptide sequence capable of specifically binding to the at least one modification of interest, and iii) a fluorescently labeled second polypeptide sequence capable of specifically binding to the first polypeptide sequence; b) combining the sample, the first polypeptide sequence and the fluorescently labeled second polypeptide sequence to produce a fluorescently labeled second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex, (step b, as claimed) and a fluorescently labeled second polypeptide sequence:first polypeptide sequence complex; c) separating the fluorescently labeled second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex, the fluorescently labeled second polypeptide sequence:first polypeptide sequence complex and the fluorescently labeled second polypeptide sequence by capillary electrophoresis; d) detecting the separated fluorescently labeled second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex by laser-induced fluorescence; and e) quantitating the separated second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex, thereby quantitating the at least one modification of interest in the nucleic acid sequence. Example 1, col. 20 up to Example 6, col. 27 provides detail steps of the method and the specific probes and polypeptides used in the method. The ‘968 Patent does not disclose fluorescence polarization. However, the ‘392 patent discloses the alternativeness of fluorescence and fluorescence polarization. It further discloses that particularly polarization is sensitive to the stability and/or conformation of the target RNA as reflected in the binding state of the probe. Accordingly, one would have been motivated to use fluorescence polarization in the method of the ‘968 Patent for the benefits derived therein as taught by the ‘392 Patent.

Response to Arguments

Claims 2, 11, 16 and 24 stand rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1 and 9 of U.S. Patent No. 6,132,968

('968 Patent), the Le patent, in view of U.S. Patent No. 6,331,392 ('392 Patent), the Laing patent. Applicant believes that the rejection of the instant claims over the '968 patent, in view of the '392 patent, is made in error, and respectfully requests withdrawal of the rejection. As a first matter, the rejection as to the '392 patent is made in error as there is no common assignee or inventor between the present invention and the Laing '392 patent. See the MPEP at 800-16.

As a second matter, claims 1 and 9 of the '968 Le patent are directed to a method for quantitating at least one modification of interest in a deoxyribonucleic acid sequence contained in a sample, which is a different invention from the methods of the present application, which is directed to a method for determining the binding affinity and/or stoichiometry of a binding complex between a binding factor and a probe.

In response, the ‘392 patent is used not as a primary reference for the obviousness double patenting rejection above, it is the ‘968 Patent which has a common inventor (Le) as the present application (sole inventor, Le). The ‘392 reference when combined with the ‘968 reference renders the argued method of quantization obvious. Applicant’s reference

to MPEP @ 800-16 is unclear as this section does not seem to exist.

The combined teachings of the references disclose all the elements of the claimed method that renders the claim prima facie obvious. {This rejection can be overcome by filing a terminal disclaimer.]

No claims are allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, James Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/TERESA WESSENDORF/
Primary Examiner, Art Unit 1639

Application Number	Application/Control No.	Applicant(s)/Patent under Reexamination	
	10/763,259	LE, XIAO-CHUN (CHRIS)	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	